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Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkh263
Advance Access publication 12 May 2004

CDC studies incorrectly summarized in 'critical review'

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Keywords: antimicrobial resistance, food animals

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Sir,

Several studies conducted by the Centers for Disease Control and Prevention (CDC) were cited in the recent article in JAC by Phillips *et al.*[1] Unfortunately, Phillips *et al.*[1] have incorrectly linked these studies to statements that do not summarize the conclusions of the authors. Among several examples, we would like to describe three incorrect summaries.

Phillips *et al.*[1] cite a CDC article in the *New England Journal of Medicine* on the emergence of multidrug-resistant *Salmonella* to support the statement: 'the resistance prevalence varies from time to time and place to place with no obvious relationship to current antibiotic usage patterns in humans or animals'.[1] To the contrary, the article by Glynn *et al.*,[2] which concerns *Salmonella* serotype Typhimurium DT104 R-type ACSSuT, states 'the proportion of isolates with five-drug pattern of resistance has increased from less than 1 percent in 1979–80 to 34 percent in 1996', and therefore describes increasing, not variable, prevalence. The article also states, 'the emergence of antimicrobial-drug resistance in *Salmonella* isolates is associated with the therapeutic use and non-therapeutic use of antimicrobial agents in food animals. Prudent use of antimicrobial agents in farm animals and more effective disease prevention on farms is necessary to reduce the dissemination of five-drug-resistant Typhimurium DT104 and to slow the evolution of resistance to additional agents in this and other strains of *Salmonella*'.[2] This statement was made based on the direct relationship between use of antimicrobial agents in food animals and the emergence of antimicrobial-resistant *Salmonella*, which results in increased transmission of these resistant pathogens to humans and increased likelihood of compromising treatment options. This relationship and its consequences are supported by numerous lines of evidence.[3]

In citing CDC authored articles in the *Journal of Infectious Diseases* and *Review of Infectious Diseases*, Phillips *et al.*[1] write: 'it might be thought that antibiotic-resistant salmonellae would have a devastating clinical effect, but this is rarely the case in developed countries'. However, neither of these articles support this statement. In the first article, Lee *et al.*[4] reported that patients with antimicrobial-resistant *Salmonella* infections were more likely to be hospitalized than those with susceptible infections, concluding that 'these data show that treatment of *Salmonella* infections may be complicated by growing resistance to clinically important antimicrobial agents and by increasing frequencies of extraintestinal complications'. In the second article, Holmberg *et al.*[5] evaluated investigations of *Salmonella* outbreaks and found that the data 'show higher rates of hospitalization and mortality associated with drug resistant than with drug-susceptible strains'. Although Phillips *et al.*[1] do not define 'devastating', we assume they would agree that excess hospitalization and mortality would merit such characterization and, rare or not, would not be a consequence that should be dismissed.

Phillips *et al.*[1] cite a CDC abstract from the 2000 International Conference on Emerging Infectious Diseases to support the statement: 'Marano *et al.*[6] reported a 4 day decrease in the duration of diarrhoea (from 12 to 8 days) for patients infected with fluoroquinolone-resistant strains treated with ciprofloxacin (but paradoxically no decrease for susceptible strains—6 days for both treated and untreated patients).' This statement does not represent conclusions from the study. In fact, Marano *et al.*[6] reported that patients with ciprofloxacin-resistant *Campylobacter* infections had a longer duration of diarrhoea than those with susceptible infections and that the longer duration occurred both among patients who took ciprofloxacin and those who did not.

There are many opportunities to reduce the overuse and misuse of antimicrobial agents in food animals. Reductions in overuse and misuse now and in the future would benefit human health by slowing the emergence and spread of resistant food-borne infections.

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Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkh262
Advance Access publication 12 May 2004

Does the use of antibiotics in food animals pose a risk to human health? A reply to critics

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Keywords: antibiotics, animal use

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Sir,

We appreciate the opportunity to reply to the criticisms[1–5] of our review of the hypothesis that the use of antibiotics in animals poses a risk to human health.[6]

We are accused of error, often not defined, making specific responses challenging. However, we were correct in referring to 'seven references' supporting the banning of growth-promoting antibiotics, noted by Dr Tollefson,[1] to which we referred in addressing 'agricultural use of antibiotics'. And we are emphatically not in error when we question received opinion that animal antibiotic use significantly harms human health harm. We intentionally did not cite every relevant paper, but cited representative papers reaching the same conclusions. We agree that Drs Karp & Engberg[3] have the correct reference for the paper by Smith *et al*.

We are accused of bias. We confess to a strong bias towards facts and data. We sought to 'redress what we perceive as an imbalance' by highlighting data that do not support the hypothesis that animal antibiotic use harms human health, often played down or even ignored by those who advise risk managers responsible for antibiotic regulation. The banning of growth-promoting antibiotics in Europe required the application of the Precautionary Principle, which conceded that data were inadequate to support such a ban, and required that good data be actively sought. In light of such data, it is our conclusion that the growth-promoter ban is still not supported by evidence that it protects human health. We believe data-based evidence to be far more important than opinion, speculation and conjecture for safeguarding human health, and accordingly biased our review toward empirical data.

Professor Collignon[2] accuses us of failing to recognize that growth-promoting antibiotics do not promote growth. We refer readers to a recent review of antibiotic effects in animals, AVCARE 2003,[7] which summarizes experience that shows that they often do. Professor Collignon also tells us that these same antibiotics do not prevent such infections as necrotic enteritis, citing the experience of the Danes.[2] However, the Danes have commendably introduced conditions of husbandry that have minimized, but not prevented, such infections, but it is naive to suggest that Denmark had no problem when the use of therapeutic antibiotics greatly increased, so dealing with the expected morbidity and mortality that might otherwise have been apparent. In contrast, neighbouring Norway reported necrotic enteritis increasing to epidemic proportions,[8] and many European countries reported increases in the use of therapeutic antibiotics after the ban.[9] It remains our conclusion that growth-promoting antibiotics continue to promote growth and to prevent important infections, albeit to different degrees in different places.

We are accused of underestimating the potential harm to human health arising from animal antibiotic use. Infections of concern are salmonellosis, campylobacteriosis and those caused by resistant enterococci. We were, of course, aware of the review by Swartz[10] cited by Dr Tollefson[1], and of his and others' difficulties in finding direct epidemiological or microbiological or clinical evidence for human harm, and consequent reliance on speculation. We continue to believe that resistance in salmonellae may be selected in animals or humans, but that its effect has been minor to undetectable since, for example, 99.96% of patients recover in the US.[11] Since systemic salmonellosis is largely a disease of the immunocompromised, some such patients succumb, although this may be more related to the underlying disease than to food-borne bacteria. Increased morbidity and mortality associated with antibiotic-resistant salmonellae in some studies seems to reflect increased virulence of resistant strains (Travers & Barza[12]) rather than resistance itself. When we said that resistant salmonellae come and go without much relation to current antibiotic usage (see Chiller *et al.*[5]) we referred to the epidemic behaviour of different DTs of *Salmonella* Typhimurium, not just DT104. Finally, we emphasized the increase of salmonella infection in humans in Denmark in 2001, to which Jensen *et al.* objected,[4] because